BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007536
Article Type:	Protocol
Date Submitted by the Author:	23-Dec-2014
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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Research methods, Rehabilitation medicine, Cardiovascular medicine
Keywords:	Chronic Obstructive Pulmonary Disease, COPD assessment test, Health status, Cardiovascular comorbidities

The impact of cardiovascular comorbidities on COPD Assessment Test (CAT) and its responsiveness to pulmonary rehabilitation in patients with moderate to very severe COPD: the protocol of the CHAnCe study

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ABSTRACT

Introduction Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality. Patients with COPD are characterized by a reduced health status, which can be easily assessed by the COPD Assessment Test (CAT). Previous studies showed that health status can be worsened by the presence of co-morbidities. However, the impact of (cardiovascular) comorbidities on health status as assessed with CAT is not sufficiently investigated. Therefore, the current study has the following objectives: 1) to study the clinical, (patho)physiological and psycho-social determinants of CAT and impact of (cardiovascular) comorbidities on health status in patients with COPD, 2) to assess the effects of pulmonary rehabilitation on CAT scores in patients with COPD, 3) to develop reference values for the CAT in Dutch elderly non-COPD subjects and 4) to validate the CAT in a broad sample of Dutch patients with COPD.

Methods and Analysis The **C**OPD, **H**ealth status **An**d **C**omorbidit**ie**s (CHAnCe) study is a monocentre study consisting of an observational cross-sectional part and a longitudinal part. Demographic and clinical characteristics were assessed in primary care, secondary care and tertiary care patients with COPD and non-COPD subjects. To assess health status the COPD Assessment test (CAT), Clinical COPD Questionnaire (CCQ) and St. George's Respiratory Questionnaire (SGRQ) were used. The longitudinal part consists of a comprehensive pulmonary rehabilitation programme in 500 tertiary care patients. For the cross-sectional part of the study 150 non-COPD subjects, 100 primary care patients and 100 secondary care patients will be assessed during a single home visit.

Ethics and dissemination The Medical Ethical Committee of the Maastricht University Medical Centre+ (MUMC+), Maastricht, the Netherlands (METC 11-3-070) has approved this study. The study has been registered at the Dutch Trial Register (NTR 3416).

BACKGROUND

Health status in patients with chronic obstructive pulmonary disease (COPD) is impaired irrespective of the degree of airflow limitation (3, 4). Therefore, optimizing health status is an important goal in COPD management (1). Indeed, according to the latest Global initiative for chronic Obstructive Lung Disease (GOLD) document, COPD assessment should include the assessment of health status as an objective in disease diagnosis and follow up (1, 2). Poor health status is multi-factorial with COPD patients, as it is associated with higher levels of dyspnea (3), reduced exercise capacity (4), symptoms of anxiety and depression (5), and frequent exacerbations and mortality (6). In addition, health status in patients with COPD can be worsened by the presence of co-morbidities like cardiovascular disease (7), and metabolic syndrome (8). Vanfleteren and colleagues showed that 97.7% of all patients with COPD have one or more comorbidities (9). In European primary care patients with COPD, the presence of ≥3 co-morbidities was associated with a worse health status (10). Cardiovascular diseases are probably the most important comorbid conditions in COPD; the risk of cardiovascular morbidity and mortality is two- to threefold higher in patients with COPD in comparison to an age- and gender-matched population without COPD (11). Probably due to shared pathophysiological mechanisms, cardiovascular comorbidities often remain unrecognized in patients with COPD (11). Rutten and colleagues reported a prevalence of 20% for previously undiagnosed heart failure in primary care patients with COPD (12). Recently, it was shown that echocardiographic abnormalities were highly prevalent in patients with COPD at the time of their first hospital admission due to a severe exacerbation (13). However, the frequency of echocardiographic abnormalities in patients with COPD referred for pulmonary rehabilitation is not known.

Health status in COPD is often assessed by disease-specific questionnaires, i.e. the St. George's Respiratory Questionnaire (SGRQ) (14) and the COPD Clinical Questionnaire (CCQ) (15). The SGRQ is reasonably time-consuming to complete, sometimes difficult to understand by patients and has a scoring algorithm that is too complex for routine use in clinical practice (16). For that reason, a simple eight-item patient-completed questionnaire, the COPD Assessment Test (CAT) was developed (17). In

the Netherlands, CCQ is also used in clinical practice. The reliability and validity of the CCQ in patients with COPD has previously been studied (16). However, less studies investigated the properties of the CAT and associations with clinical, physiological and psychological outcomes in COPD. Also, there was a lack of studies about CAT in the Dutch population. Therefore, the **C**OPD, **H**ealth status **An**d **C**omorbidit**ie**s (CHAnCe) study was initiated and the following objectives were formulated:

1. To study the clinical, (patho)physiological and psycho-social determinants of CAT and impact of (cardiovascular) comorbidities on health status in patients with COPD.
2. To assess the effects of pulmonary rehabilitation on CAT scores in patients with COPD.
3. To develop reference values for the CAT by comparing COPD patients using Dutch elderly non-COPD subjects.
4. To validate the COPD Assessment Test in a broad sample of Dutch patients with COPD.

METHODS

Study design

The current study is a monocenter, observational study consisting of an observational cross-sectional part (objectives 1, 3 and 4) and a longitudinal part (objective 2), see figure 1.

Study population

Patients will be recruited from primary (general practitioners), secondary (chest physicians) and tertiary (pulmonary rehabilitation) care. The inclusion of subjects started in April 2012. The inclusion of the subjects from the tertiary care setting has been completed mid-2014. It is expected that the inclusion of the non-COPD subjects and subjects from the primary and secondary care setting will be completed early 2015. Figure 1 shows an overview of the study objectives and study population. In order to study objectives 1 and 2, 500 patients with COPD referred for clinical assessment and pulmonary rehabilitation to CIRO+, Horn, The Netherlands will be recruited (18). In order to examine objective 3 (see figure 1) 150 non-COPD subjects will be recruited in general practitioners (GP's) via `Registration Network of Family Practices (RNH)' (19). Objective 4 (see figure 1) will be studied by

assessing 100 patients with COPD from primary care setting (recruited in general practitioners via RNH) and 100 patients with COPD from secondary care setting (partly recruited via RNH and partly at the outpatient pulmonary consultation of Maastricht University Medical Center (MUMC) Maastricht). Primary care patients will be eligible if exclusively treated by a GP without being treated by a chest physician or previously been treated in tertiary care in the previous five years. Secondary care patients will be eligible if only being treated by a chest physician and not been treated in tertiary care for the previous five years. In addition, 500 patients with COPD from tertiary care setting will be included for the fourth objective. The 500 tertiary care patients that will be tested for objectives 3 and 4 will be part of the sample for objectives 1 and 2. All study procedures will conducted by CIRO+.

Study procedure

Non-COPD subjects, primary care patients and part of the secondary care patients will be recruited via RNH. RNH will provide the contact details of participating GPs. Accordingly, the investigator will contact the responsible GP practices if they are willing to participate. After the GP's approval of collaboration, medical records of the practice are screened using the RNH software according to the eligibility criteria for the study. Following approval of the responsible GP, the investigators from CIRO+ will send a letter in the name of the GP, introducing the research and asking whether the patient wants to participate. In case of patients' consent, a response letter with contact details will be returned to CIRO+ Horn, enabling the investigator to contact the participant and check the eligibility criteria via phone. If the patients is still eligible and interested, an appointment for the home visit will be scheduled. The remaining secondary care patients will be recruited by chest physicians from an academic hospital (Maastricht University Medical Center, MUMC). During their outpatient pulmonary consultations, the chest physicians will ask the patient if he/she is interested in participating in the study. If so, the CIRO+ investigators will be provided with the contact details, will contact the potential candidates and possibly schedule an appointment. All patients will be asked to give written informed consent during the home visit together. Patients from primary and secondary care and non-COPD subjects will be visited at their home. A home visit will last approximately one and a half to two hours.

If it is not possible to conduct the visit in their home environment, the participant will be asked to come to CIRO+ for two hours. Tertiary care patients will be recruited at CIRO+ during their pre-rehabilitation assessment. Baseline and outcome assessment data will be collected in these patients (see figure 1). CIRO+ is providing a state-of-the-art interdisciplinary pulmonary rehabilitation program for patients with COPD in line with the latest ATS/ERS Statement on Pulmonary Rehabilitation (20). Patients are referred for inpatient (8 weeks) or outpatient (16 weeks) pulmonary rehabilitation based on their pre-rehabilitation assessment (18). The pulmonary rehabilitation programme in this study is part of the usual care of these patients at CIRO+.

Eligibility criteria

Patients are eligible if they fulfill the following criteria:

1. Age 40-85 years.
2. A diagnosis of COPD according to GOLD guidelines (2).

Patients with COPD from the tertiary care setting also have to fulfil the following criteria:

3. Referral for assessment and pulmonary rehabilitation in CIRO+ by a chest physician.

Non-COPD subjects are eligible if they fulfill the following criteria:

1. Age 40-85 years.
2. Post-bronchodilator $FEV_1/FVC \geq 70\%$.
3. Healthy, as judged by the investigator and determined by medical history and physical examination.

Exclusion criteria for the patients with COPD:

1. A history of asthma, lung cancer, sarcoidosis, tuberculosis, lung fibrosis, cystic fibrosis or any other significant respiratory disease.
2. A moderate or severe exacerbation or pneumonia requiring systemic corticosteroids, antibiotics or hospitalisation during the last 4 weeks.

3. Having undergone lung surgery (e.g. lung volume reduction, lung transplantation).
4. Any clinically relevant disease which in the opinion of the investigator may influence the results of the study.
5. Malignancy within the last 5 years.
6. For primary care patients: treatment by respiratory physician in secondary or tertiary care.
   For secondary care patients: treatment in tertiary care setting in the previous 5 years.

Exclusion criteria for the non-COPD subjects:

1. A history of COPD, asthma, lung cancer, sarcoidosis, tuberculosis, lung fibrosis, cystic fibrosis or any other significant respiratory disease, lung surgery in the past.
2. Chronic heart failure in medical history.
3. Any clinically relevant disease which in the opinion of the investigator may influence the results of the study.
4. Malignancy within the last 5 years.

Outcomes

The following table provides an overview of the recorded variables for each group.

Table 1. Outcome measures per healthcare group

Outcomes	Non-COPD	Primary care	Secondary care	Tertiary care (pre rehabilitation)	Tertiary care (post rehabilitation)
Demographics, including age, gender, height, weight, marital status, ethnic origin.	Y	Y	Y	Y	Y
Smoking history: current smoking and pack years	Y	Y	Y	Y	Y
Medical history, including current medication	Y	Y	Y	Y	N
COPD history: number of exacerbations and hospitalisations for COPD (<12 months)	Y	Y	Y	Y	Y
Use of long-term oxygen or non-invasive ventilation	Y	Y	Y	Y	Y
Lung function: post-bronchodilator (salbutamol) spirometry measured by a handheld SpiroPro Viasys	Y	Y	Y	N	N
Lung function: post-bronchodilator (salbutamol) spirometry measured by standardized equipment of Masterlab®, Jaeger, Germany whole-body plethysmography, diffusing capacity for carbon monoxide (31)	N	N	N	Y	Y
Degree of self-perceived physical and psychological symptoms [a]	Y	Y	Y	Y	N

Physical examination including vital signs: pulse, blood pressure, saturation	Y	Y	Y	Y	Y
Charlson co-morbidity index **(21)**	Y	Y	Y	Y	Y
Medical Research Council (MRC) dyspnoea grading **(22)** and New York Heart Association (NYHA) Functional Classification **(23)**	Y	Y	Y	Y	Y
Health status questionnaires: SGRQ-C, CAT, and CCQ **(24)**.	Y	Y	Y	Y	Y
Hospital Anxiety and Depression Scale **(25)**	Y	Y	Y	Y	Y
Daily physical functioning: timed 'up-and-go' test **(26)**	Y	Y	Y	Y	Y
Care Dependency Scale **(27)**	Y	Y	Y	Y	Y
Coping strategies: Utrecht Coping List (37)	N	N	N	Y	Y
Body composition: fat-free mass, fat mass using bioelectrical impedance assessment **(28)**	Y	Y	Y	Y	N
Body composition: whole-body/local dual energy x-ray absorptiometry (DEXA) scan (32)	N	N	N	Y	Y
Systemic inflammation: hsCRP	N	N	N	Y	Y
Six Minute Walk test (2x at baseline) (33)	N	N	N	Y	Y
Constant work-rate bicycle test (34) and cardio pulmonary exercise test	N	N	N	Y	Y
Daily physical activity level using a validated accelerometer (35)	N	N	N	Y	Y
Problematic activities of daily life: Canadian Occupational Performance Measure (36)	N	N	N	Y	Y
Lower-limb muscle function: peak isokinetic quadriceps strength using a biodex (38)	N	N	N	Y	Y
Echocardiography	N	N	N	Y	N
Electrocardiography (39)	N	N	N	Y	Y
NT-proBNP and other cardiovascular markers (to be determined)	N	N	N	Y	Y
Biomarkers metabolic syndrome (40): fasting glucose, cholesterol, HDL, LDL, triglycerides	N	N	N	Y	Y

Y = measurement conducted
N = measurement not conducted
[a] Patient-completed checklist referring to dyspnoea, fatigue, cough, muscle strength, appetite, insomnia, depression, anxiety, panic attacks, pain, mouth soreness, itching, edema, thirst, muscle cramps, restless legs, dizziness, pain on the chest and frequency of urination with visual analogue scales to score the severity of the complaint (questionnaire is approved by the Medical Ethical Committee of the Maastricht University Medical Centre, METC 07-3-054).

Data management and statistics

Data will be screened for missing values. In order to reduce the number of missing data, a researcher will be present when filling out the questionnaires. When there is missing data in the questionnaires,

the missing values will be processed according to the guidelines of the different questionnaires. This will be done for every variable and participant. Other missing values will excluded by list wise deletion.

All variables will be tested for normality. Descriptive statistics, including means (SD), medians (IQR) and frequencies, will be applied. Continuous variables will be presented as mean (95% confidence interval). To answer objective 1, the differences between groups will be assessed with unpaired Student's t-test. Multiple clinical outcomes will be tested in their association with CAT scores via multiple ordinary least squares (OLS) regression models. For objective 2, an analysis of variance of repeated measurement will be done to measure the change in CAT scores and an one-way ANOVA or two-tailed paired t-test will be used to determine changes in CAT scores following a comprehensive pulmonary rehabilitation program. To examine objective 3, the characteristics and CAT scores of the healthy subjects will be tested for normality with the Kolmogorov-Smirnov test. To validate and look at reference values for the CAT the upper limit of the 95% confidence interval of the CAT scores will be determined in the non-COPD subjects. All scores above this value will be defined as 'an abnormal health status'. For objective 4, differences in CAT scores and other clinical characteristics between primary care and secondary care, and tertiary care COPD samples will be assessed by using a one-way analysis of variances (ANOVA). Finally, the scores of the CAT between the groups of primary, secondary, and tertiary care, and non-COPD subjects will be examined. All statistics will be done using SPSS V.20.0 and GraphPad Prism. A p-value of less than 0.05 was considered statistically significant.

Dissemination

Study data will be stored in the data centre of CIRO+. The investigator will ensure that all data in the data centre are accurate and is responsible for the monitoring of the data collection. Results will be presented at (inter)national conferences and will be submitted for publication in peer-reviewed journals. Participants are given the opportunity to be informed about the results of the study.

DISCUSSION

The current study has been designed to study the validity and responsiveness to pulmonary rehabilitation of CAT in a Dutch population. Initially, the clinical, (patho)physiological and psycho-social determinants of CAT and impact of (cardiovascular) comorbidities on health status in patients with COPD will be examined. In addition, reference values for the CAT will be developed by comparing COPD patients using Dutch elderly non-COPD. The strengths and limitations of the current study will be described below.

Strengths

In the current literature, most COPD studies focus on patients from secondary care or tertiary care (29). To our knowledge, this is the first study including patients with COPD treated in primary care as well as patients with COPD treated in secondary and tertiary care. In addition, the current study includes non-COPD subjects enabling a comparison between primary, secondary and tertiary care patients and non-COPD subjects, regarding e.g. health status, mood status and functional status. Consequently, reference values for the CAT for Dutch elderly non-COPD subjects can be determined. Additionally, the majority of the measurements will be done with the same devices. This provides a high reliability, despite the fact that the measurements have been carried out at different places. Furthermore, inter-observer bias is minimized, because all measurements in the non-COPD subjects, primary care and secondary care patients will been performed by one researcher. Furthermore, as mentioned before, patients with COPD have a two- to threefold higher chance to develop cardiovascular morbidity and mortality risk than people without COPD (11) underlying the importance to assess these comorbid conditions carefully. The current study is the first investigating a wide range of (extra)pulmonary parameters providing the possibility to study the individual effect of cardiovascular comorbidities on outcomes, e.g. health status. Finally, patients are recruited from eight different GP practices (RNH affiliated), an academic hospital and a pulmonary rehabilitation centre (CIRO+) increasing the internal and external validity.

Limitations

The results of the current study will be subject to several limitations. *First*, the study sample consists of a convenience sample: possibly in all four healthcare groups the patients with more symptoms, lack of motivation or more severe COPD are less willing to participate in the study, which can lead to selection bias. Consequently, outcomes can be more favourable. To limit selection bias as much as possible, all non-COPD subjects, primary care patients and secondary care patients will be randomly selected by their GP and chest physician. *Second*, health status may seem a subjective measure. Questionnaires addressing health status usually look at the emotional, psychological and physical effect of a disease. Measuring health status implies quantifying the impact of the illness on health, wellbeing and daily life, in a standardized and objective manner. According to Jones, the end product doesn't give a clinical impression, because an impaired health status may express itself differently in each patient. However, these questionnaires make it possible to compare health status in patients with COPD (30). *Third*, it is not possible to perform the spirometry measurement with the same devices. The spirometry performed in tertiary patients with COPD will be done at CIRO+ as a part of their usual care with the standardized spirometer equipment of Masterlab. However, this device is not portable, making it impossible to be taken to home visits. For this reason we have chosen for the SpiroPro Viasys to measure lung function in non-COPD subjects and primary and secondary care patients. Both devices are valid and reliable instruments (31, 32) and are currently used in COPD studies (33, 34). *Finally*, measurements in primary and secondary care patients as well as non-COPD subjects will only be conducted cross-sectionally not providing the possibility to determine causality.

Clinical consequences

The current study is very likely to have clinical implications. Initially, it will give more insight in understanding the systemic effects of COPD, especially on the impact of (cardiovascular) comorbidities on health status. By performing an echocardiography, we will be able to examine cardiac

abnormalities, e.g. an impaired systolic left ventricular function, valvular abnormalities or increased right ventricular pressures in relation to clinical outcomes in COPD. This will enable better monitoring of patients and ensure patient safety during pulmonary rehabilitation. Ultimately, patients at risk can receive more personalized, predictive, preventive and participatory (P4 medicine) care, e.g. to prevent a worsening and/or optimize health status (35). In addition, the current study will examine whether the CAT is a valid measurement to assess health status in Dutch patients and local reference values for clinical practice will be developed. Moreover, by comparing non-COPD subjects and primary, secondary and tertiary care COPD patients, this study will increased our understanding of similarities and differences between the various health care categories in the Netherlands.

Conclusion

To conclude, health status is an important patient-related outcome in COPD. Thus, understanding the validity, responsiveness and clinical determinants of the COPD assessment test (CAT) is essential for the management of patients with this disease. The CHAnCe study will greatly extend the current knowledge on CAT in patients with COPD and non-COPD. In this article the study protocol was described and possible strengths and limitations outlined.

Footnotes

Contributors DES, SW, EFMW, FMEF and MAS contributed to the writing of this protocol article.

Every author read and approved the final version.

Funding The CAT study was supported by the Lung Foundation Netherlands (3.4.10.015) and GlaxoSmithKline (SCO115406).

Competing interests None.

Patient consent Obtained

Ethics approval The Medical Ethical Committee of the Maastricht University Medical Centre+ (MUMC+), Maastricht, the Netherlands (METC 11-3-070) has approved this study. The study has been registered at the Dutch Trial Register (NTR 3416).

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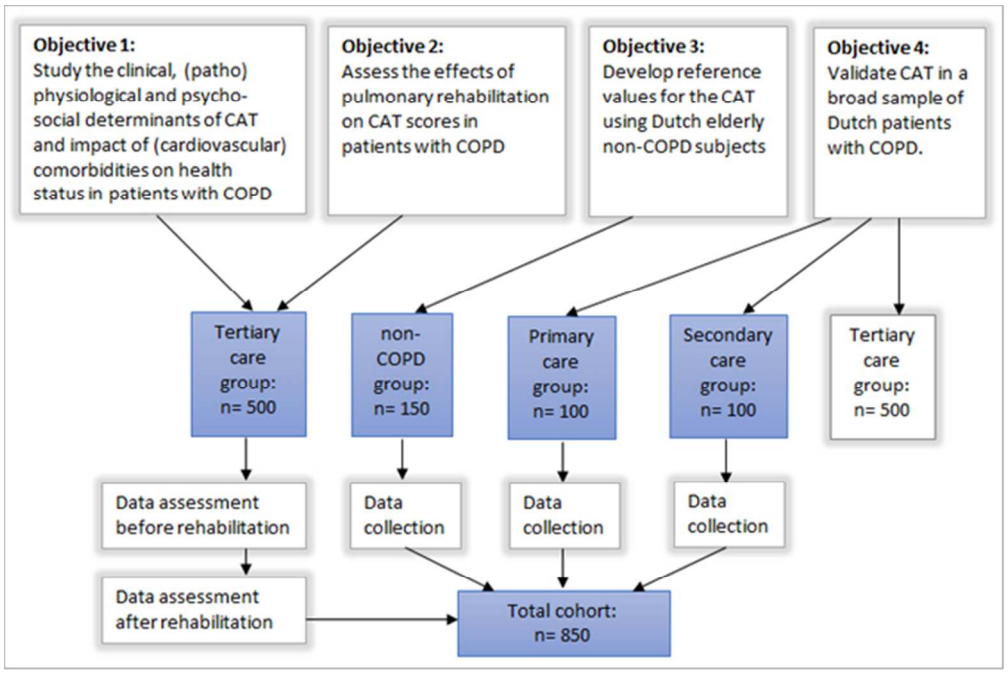
Outcomes	Non-COPD	Primary care	Secondary care	Tertiary care (pre rehabilitation)	Tertiary care (post rehabilitation)
Demographics, including age, gender, height, weight, marital status, ethnic origin.	Y	Y	Y	Y	Y
Smoking history: current smoking and pack years	Y	Y	Y	Y	Y
Medical history, including current medication	Y	Y	Y	Y	N
COPD history: number of exacerbations and hospitalisations for COPD (<12 months)	Y	Y	Y	Y	Y
Use of long-term oxygen or non-invasive ventilation	Y	Y	Y	Y	Y
Lung function: post-bronchodilator (salbutamol) spirometry measured by a handheld SpiroPro Viasys	Y	Y	Y	N	N
Lung function: post-bronchodilator (salbutamol) spirometry measured by standardized equipment of Masterlab®, Jaeger, Germany whole-body plethysmography, diffusing capacity for carbon monoxide (31)	N	N	N	Y	Y
Degree of self-perceived physical and psychological symptoms [a]	Y	Y	Y	Y	N
Physical examination including vital signs: pulse, blood pressure, saturation	Y	Y	Y	Y	Y
Charlson co-morbidity index **(21)**	Y	Y	Y	Y	Y
Medical Research Council (MRC) dyspnoea grading **(22)** and New York Heart Association (NYHA) Functional Classification **(23)**	Y	Y	Y	Y	Y
Health status questionnaires: SGRQ-C, CAT, and CCQ **(24)**.	Y	Y	Y	Y	Y
Hospital Anxiety and Depression Scale **(25)**	Y	Y	Y	Y	Y
Daily physical functioning: timed 'up-and-go' test **(26)**	Y	Y	Y	Y	Y
Care Dependency Scale **(27)**	Y	Y	Y	Y	Y
Coping strategies: Utrecht Coping List (37)	N	N	N	Y	Y
Body composition: fat-free mass, fat mass using bioelectrical impedance assessment **(28)**	Y	Y	Y	Y	N
Body composition: whole-body/local dual energy x-ray absorptiometry (DEXA) scan (32)	N	N	N	Y	Y
Systemic inflammation: hsCRP	N	N	N	Y	Y
Six Minute Walk test (2x at baseline) (33)	N	N	N	Y	Y
Constant work-rate bicycle test (34) and cardio pulmonary exercise test	N	N	N	Y	Y
Daily physical activity level using a validated accelerometer (35)	N	N	N	Y	Y
Problematic activities of daily life: Canadian Occupational Performance Measure (36)	N	N	N	Y	Y
Lower-limb muscle function: peak isokinetic quadriceps strength using a biodex (38)	N	N	N	Y	Y
Echocardiography	N	N	N	Y	N
Electrocardiography (39)	N	N	N	Y	Y
NT-proBNP and other cardiovascular markers (to be determined)	N	N	N	Y	Y
Biomarkers metabolic syndrome (40): fasting glucose, cholesterol, HDL, LDL, triglycerides	N	N	N	Y	Y

Y= measurement conducted

N= measurement not conducted

[a] Patient-completed checklist referring to dyspnoea, fatigue, cough, muscle strength, appetite, insomnia, depression, anxiety, panic attacks, pain, mouth soreness, itching, edema, thirst, muscle cramps, restless legs, dizziness, pain on the chest and frequency of urination with visual analogue scales to score the severity of the complaint (questionnaire is approved by the Medical Ethical Committee of the Maastricht University Medical Centre, METC 07-3-054).



Flow diagram of subject participation

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3 and 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper	Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4, 5 and 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 6 and 7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Inapplicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7 and 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5, 6, 7 and 8
Bias	9	Describe any efforts to address potential sources of bias	Page 10 and 11
Study size	10	Explain how the study size was arrived at	Inapplicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Inapplicable
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	Page 8 and 9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Inapplicable
		(*e*) Describe any sensitivity analyses	Page 9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Inapplicable, study not yet performed
		(b) Give reasons for non-participation at each stage	Inapplicable, study not yet performed
		(c) Consider use of a flow diagram	Page 16
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Inapplicable, study not yet performed
		(b) Indicate number of participants with missing data for each variable of interest	Inapplicable, study not yet performed
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Page 7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Inapplicable, study not yet performed
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Inapplicable, study not yet performed
		Cross-sectional study—Report numbers of outcome events or summary measures	Inapplicable, study not yet performed
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Inapplicable, study not yet performed
		(*b*) Report category boundaries when continuous variables were categorized	Inapplicable, study not yet performed
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Inapplicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Inapplicable, study not yet performed
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 11 and 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

BMJ Open

The impact of cardiovascular comorbidities on COPD Assessment Test (CAT) and its responsiveness to pulmonary rehabilitation in patients with moderate to very severe COPD: the protocol of the Chance study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-007536.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Apr-2015
Complete List of Authors:	Smid, Dionne; Ciro+, centre of expertise for chronic organ failure, Department of Research and Education Wilke, Sarah; Ciro+, centre of expertise for chronic organ failure, Department of Research and Education Jones, Paul; St Georges, Univeersity of London Muris, Jean; Maastricht University, Family Medicine Wouters, Emiel; Ciro+, centre of expertise for chronic organ failure, Department of Research and Education; Maastricht University Medical Centre, Respiratory Medicine Franssen, Frits; Ciro+, centre of expertise for chronic organ failure, Department of Research and Education; Maastricht University Medical Centre, Respiratory Medicine Spruit, Martijn; CIRO, Program Development Centre
Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Research methods, Rehabilitation medicine, Cardiovascular medicine
Keywords:	Chronic Obstructive Pulmonary Disease, COPD assessment test, Health status, Cardiovascular comorbidities

The impact of cardiovascular comorbidities on COPD Assessment Test (CAT) and its responsiveness to pulmonary rehabilitation in patients with moderate to very severe COPD: the protocol of the Chance study

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ABSTRACT

Introduction Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality. Patients with COPD are characterized by a reduced health status, which can be easily assessed by the COPD Assessment Test (CAT). Previous studies show that health status can be worsened by the presence of co-morbidities. However, the impact of cardiovascular comorbidities on health status as assessed with CAT is not sufficiently investigated. Therefore, the current study has the following objectives: 1) to study the clinical, (patho)physiological and psycho-social determinants of CAT and impact of previously established and/or newly diagnosed cardiovascular comorbidities on health status in tertiary care patients with COPD, 2) to assess the effects of pulmonary rehabilitation on CAT scores in patients with COPD, 3) to develop reference values for the CAT in Dutch elderly non-COPD subjects and 4) to validate the CAT in a broad sample of Dutch patients with COPD.

Methods and Analysis The **C**OPD, **H**ealth status **an**d **C**omorbidit**ie**s (Chance) study is a monocentre study consisting of an observational cross-sectional part and a longitudinal part. Demographic and clinical characteristics will be assessed in primary care, secondary care and tertiary care patients with COPD and non-COPD subjects. To assess health status the COPD Assessment test (CAT), Clinical COPD Questionnaire (CCQ) and St. George's Respiratory Questionnaire (SGRQ) will be used. The longitudinal part consists of a comprehensive pulmonary rehabilitation programme in 500 tertiary care patients. For the cross-sectional part of the study 150 non-COPD subjects, 100 primary care patients and 100 secondary care patients will be assessed during a single home visit.

Ethics and dissemination The Medical Ethical Committee of the Maastricht University Medical Centre+ (MUMC+), Maastricht, the Netherlands (METC 11-3-070) has approved this study. The study has been registered at the Dutch Trial Register (NTR 3416).

BACKGROUND

Health status in patients with chronic obstructive pulmonary disease (COPD) is impaired irrespective of the degree of airflow limitation (1). Therefore, optimizing health status is an important goal in COPD management (2). Indeed, according to the latest Global initiative for chronic Obstructive Lung Disease (GOLD) document, COPD assessment should include the assessment of health status as an objective in disease diagnosis and follow up (3). Poor health status is multi-factorially determined in COPD patients, as it is associated with higher levels of dyspnea (4), reduced exercise capacity (5), symptoms of anxiety and depression (6), and frequent exacerbations and mortality (7). In addition, health status in patients with COPD can be worsened by the presence of co-morbidities (8). Vanfleteren and colleagues showed that 97.7% of all patients with COPD have one or more comorbidities (9). In European primary care patients with COPD, the presence of ≥3 co-morbidities was associated with a worse health status (10). Cardiovascular diseases are presumably the most important comorbid conditions in COPD. The risk of cardiovascular morbidity and mortality is two- to threefold higher in patients with COPD in comparison to an age- and gender-matched population without COPD (11). Probably due to shared pathophysiological mechanisms, cardiovascular comorbidities often remain unrecognized in patients with COPD (11). Rutten and colleagues reported a prevalence of 20% for previously undiagnosed heart failure in primary care patients with COPD (12). In addition, it was recently shown that echocardiographic abnormalities were highly prevalent in patients with COPD at the time of their first hospital admission due to a severe exacerbation (13). However, the frequency of echocardiographic abnormalities in patients with COPD referred for pulmonary rehabilitation is not known.

Health status in COPD is often assessed by disease-specific questionnaires, i.e. the St. George's Respiratory Questionnaire (SGRQ) (14) and the COPD Clinical Questionnaire (CCQ) (15). The SGRQ is reasonably time-consuming to complete, sometimes difficult to understand by patients and has a scoring algorithm that is too complex for routine use in clinical practice (16). In the Netherlands, the

CCQ is commonly used in clinical practice. The reliability and validity of the CCQ in patients with COPD have previously been studied (16). In addition, a simple eight-item patient-completed questionnaire, the COPD Assessment Test (CAT) was developed some years ago (17). However, to a lesser extent studies investigated the properties of the CAT and associations with clinical, physiological and psychological outcomes in COPD. Additionally, during the period that the current study protocol was designed few studies about CAT in the Dutch population were published. Therefore, the **C**OPD, **H**ealth status **an**d **C**omorbidit**ie**s (Chance) study was initiated and the following objectives were formulated:

1. To study the clinical, (patho)physiological and psycho-social determinants of CAT and impact of previously established and/or new diagnosed cardiovascular comorbidities on health status in tertiary care patients with COPD.
2. To assess the effects of pulmonary rehabilitation on CAT scores in patients with COPD.
3. To develop reference values for the CAT by comparing COPD patients using Dutch elderly non-COPD subjects.
4. To validate the COPD Assessment Test in a broad sample of Dutch patients with COPD.

METHODS

Study design

The current study is a monocenter, observational study consisting of an observational cross-sectional part (objectives 1, 3 and 4) and a longitudinal part (objective 2), see figure 1.

Study population

Patients will be recruited from primary (general practitioners), secondary (chest physicians) and tertiary (pulmonary rehabilitation) care. The inclusion of subjects started in April 2012. The inclusion of the subjects from the tertiary care setting was completed in September 2014. It is expected that the inclusion of the non-COPD subjects and subjects from the primary and secondary care setting will be completed early 2015. Figure 1 shows an overview of the study objectives and study population. In

order to study objectives 1 and 2, 500 patients with COPD referred for clinical assessment and pulmonary rehabilitation to CIRO+, Horn, The Netherlands will be recruited (18). In order to examine objective 3 (see figure 1) 150 non-COPD subjects will be recruited in general practitioners (GP's) via `Registration Network of Family Practices (RNH)' (19). Objective 4 (see figure 1) will be studied by assessing 100 patients with COPD from primary care setting (recruited in general practitioners via RNH) and 100 patients with COPD from secondary care setting (partly recruited via RNH and partly at the outpatient pulmonary consultation of Maastricht University Medical Center (MUMC) Maastricht). Primary care patients are eligible if they are exclusively treated by a GP without being treated by a chest physician or have been treated in tertiary care in the previous five years. Secondary care patients are eligible when only being treated by a chest physician and have not been treated in tertiary care for the previous five years. In addition, 500 patients with COPD from tertiary care setting will be included for the fourth objective. The 500 tertiary care patients that will be tested for objectives 3 and 4 will be part of the sample for objectives 1 and 2. All study procedures will conducted by CIRO+.

Study procedure

Non-COPD subjects, primary care patients and part of the secondary care patients will be recruited via RNH. RNH will provide the contact details of participating GPs. Accordingly, the investigator will contact the responsible GP practices if they are willing to participate. After the GP's approval of collaboration, medical records of the practice are screened using the RNH software, according to the eligibility criteria for the study. Following approval of the responsible GP, the investigators from CIRO+ will send a letter to every eligible subject on behalf of the GP, introducing the research and asking whether the patient wants to participate. In case of patients' consent, a response letter with contact details will be returned to CIRO+ Horn, enabling the investigator to contact the participant and check the eligibility criteria via phone. If the patients is still eligible and interested, an appointment for the home visit will be scheduled. The remaining secondary care patients will be recruited by chest

physicians from an academic hospital (Maastricht University Medical Center, MUMC). During their outpatient pulmonary consultations, the chest physicians will ask the patient if he/she is interested in participating in the study. If so, the CIRO+ investigators will be provided with the contact details, will contact the potential candidates and possibly schedule an appointment. Patients from primary and secondary care and non-COPD subjects will be visited at their home. A home visit will last approximately one and a half to two hours. If it is not possible to conduct the visit in their home environment, the participant will be asked to come to CIRO+ for two hours. All patients will be asked to give written informed consent at the beginning of the home visit or visit to CIRO+. Tertiary care patients will be recruited at CIRO+ during their pre-rehabilitation assessment. Eligible patients will be asked if they are willing to participate in the study. After approval and signing the informed consent, required data will be gathered. In these patients, baseline and outcome assessment data will be collected (see figure 1). CIRO+ is providing a state-of-the-art interdisciplinary pulmonary rehabilitation program for patients with COPD in line with the latest ATS/ERS Statement on Pulmonary Rehabilitation (20). Patients are referred for inpatient (8 weeks) or outpatient (16 weeks) pulmonary rehabilitation based on their pre-rehabilitation assessment (18). The pulmonary rehabilitation programme in this study is part of the usual care of these patients at CIRO+.

Eligibility criteria

Patients are eligible if they fulfill the following criteria:

1. Age 40-85 years.
2. A diagnosis of COPD according to GOLD guidelines (3).

Patients with COPD from the tertiary care setting also have to fulfil the following criteria:

3. Referral for assessment and pulmonary rehabilitation in CIRO+ by a chest physician.

Non-COPD subjects are eligible if they fulfill the following criteria:

1. Age 40-85 years.
2. Post-bronchodilator $FEV_1/FVC \geq 70\%$.

3. Healthy, as judged by the investigator and determined by medical history and physical examination (specified under the heading 'exclusion criteria for the non-COPD subjects').

Exclusion criteria for the patients with COPD:

1. A history of asthma, lung cancer, sarcoidosis, tuberculosis, lung fibrosis, cystic fibrosis or any other significant respiratory disease.
2. A moderate or severe exacerbation or pneumonia requiring systemic corticosteroids, antibiotics or hospitalisation during the last 4 weeks.
3. Having undergone lung surgery (e.g. lung volume reduction, lung transplantation).
4. Any clinically relevant disease which in the opinion of the investigator may influence the results of the study, referring to diseases influencing health status not related to symptoms of COPD.
5. Malignancy within the last 5 years.
6. For primary care patients: treatment by respiratory physician in secondary or tertiary care.
   For secondary care patients: treatment in tertiary care setting in the previous 5 years.

Exclusion criteria for the non-COPD subjects:

1. A history of COPD, asthma, lung cancer, sarcoidosis, tuberculosis, lung fibrosis, cystic fibrosis or any other significant respiratory disease, lung surgery in the past.
2. Chronic heart failure in medical history.
3. Any clinically relevant disease which in the opinion of the investigator may influence the results of the study, referring to diseases influencing health status not related to symptoms of COPD.
4. Malignancy within the last 5 years.

Outcomes

Table 1 provides an overview of the recorded variables for each group.

Table 1. Outcome measures per healthcare group

Outcomes	Non-COPD	Primary care	Secondary care	Tertiary care (pre rehabilitation)	Tertiary care (post rehabilitation)
Demographics, including age, gender, height, weight, marital status, ethnic origin.	Y	Y	Y	Y	Y
Smoking history: current smoking and pack years	Y	Y	Y	Y	Y
Medical history, including current medication	Y	Y	Y	Y	N
COPD history: number of exacerbations and hospitalisations for COPD (<12 months)	Y	Y	Y	Y	Y
Use of long-term oxygen or non-invasive ventilation	Y	Y	Y	Y	Y

Lung function: post-bronchodilator (salbutamol) spirometry measured by a handheld SpiroPro Viasys	Y	Y	Y	N	N
Lung function: post-bronchodilator (salbutamol) spirometry measured by standardized equipment of Masterlab®, Jaeger, Germany whole-body plethysmography, diffusing capacity for carbon monoxide (31)	N	N	N	Y	Y
Degree of self-perceived physical and psychological symptoms [a]	Y	Y	Y	Y	N
Physical examination including vital signs: pulse, blood pressure, saturation	Y	Y	Y	Y	Y
Charlson co-morbidity index **(21)**	Y	Y	Y	Y	Y
Modified Medical Research Council (mMRC) dyspnoea grading **(22)** and New York Heart Association (NYHA) Functional Classification **(23)**	Y	Y	Y	Y	Y
Health status questionnaires: SGRQ-C, CAT, and CCQ **(24)**.	Y	Y	Y	Y	Y
Hospital Anxiety and Depression Scale **(25)**	Y	Y	Y	Y	Y
Daily physical functioning: timed 'up-and-go' test **(26)**	Y	Y	Y	Y	Y
Care Dependency Scale **(27)**	Y	Y	Y	Y	Y
Coping strategies: Utrecht Coping List (37)	N	N	N	Y	Y
Body composition: fat-free mass, fat mass using bioelectrical impedance assessment **(28)**	Y	Y	Y	Y	N
Body composition: whole-body/local dual energy x-ray absorptiometry (DEXA) scan (32)	N	N	N	Y	Y
Systemic inflammation: hsCRP	N	N	N	Y	Y
Six Minute Walk test (2x at baseline) (33)	N	N	N	Y	Y
Constant work-rate bicycle test (34) and cardio pulmonary exercise test	N	N	N	Y	Y
Daily physical activity level using a validated accelerometer (35)	N	N	N	Y	Y
Problematic activities of daily life: Canadian Occupational Performance Measure (36)	N	N	N	Y	Y
Lower-limb muscle function: peak isokinetic quadriceps strength using a biodex (38)	N	N	N	Y	Y
Echocardiography	N	N	N	Y	N
Electrocardiography (39)	N	N	N	Y	Y
NT-proBNP and other cardiovascular markers (to be determined)	N	N	N	Y	Y
Biomarkers metabolic syndrome (40): fasting glucose, cholesterol, HDL, LDL, triglycerides	N	N	N	Y	Y
Y = measurement conducted N = measurement not conducted					

[a] Patient-completed checklist referring to dyspnoea, fatigue, cough, muscle strength, appetite, insomnia, depression, anxiety, panic attacks, pain, mouth soreness, itching, edema, thirst, muscle cramps, restless legs, dizziness, pain on the chest and frequency of urination with visual analogue scales to score the severity of the complaint (questionnaire is approved by the Medical Ethical Committee of the Maastricht University Medical Centre, METC 07-3-054).

Sample size calculation

The protocol has been developed in 2012. At that time, the minimally clinically important difference (MCID) was not yet established for the CAT. An estimation of the MCID was made to calculate the sample size for the current study. During the study period, the MCID of the CAT was set on 2 points (29). Subsequently, the sample size calculation was adjusted based on the most recent findings (calculated with the program G*power 3.1.9). Resulting in a study population of 150 non-COPD subjects, 100 primary care patients, 100 secondary care patients and 500 tertiary care patients. The full sample size calculation is accessible via the online supplement.

Data management and statistics

Data will be screened for missing values. In order to reduce the number of missing data, a researcher will be present when filling out the questionnaires. When there is missing data in the questionnaires, the missing values will be processed according to the guidelines of the different questionnaires. This will be done for every variable and participant. Other missing values will be excluded by list wise deletion.

All variables will be tested for normality. Descriptive statistics, including means (SD), medians (IQR) and frequencies, will be applied. Continuous variables will be presented as mean (95% confidence interval). To answer objective 1, the differences between groups will be assessed with unpaired Student's t-test. Multiple clinical outcomes will be tested in their association with CAT scores via multiple ordinary least squares (OLS) regression models. For objective 2, an analysis of variance of repeated measurement will be done to measure the change in CAT scores and an one-way ANOVA or two-tailed paired t-test will be used to determine changes in CAT scores following a comprehensive

pulmonary rehabilitation program. To examine objective 3, the characteristics and CAT scores of the non-COPD subjects will be tested for normality with the Kolmogorov-Smirnov test. To validate and look at reference values for the CAT the upper limit of the 95% confidence interval of the CAT scores will be determined in the non-COPD subjects. All scores above this value will be defined as 'an abnormal health status'. For objective 4, differences in CAT scores and other clinical characteristics between primary care and secondary care, and tertiary care COPD samples will be assessed by using a one-way analysis of variances (ANOVA). Finally, the scores of the CAT between the groups of primary, secondary, and tertiary care, and non-COPD subjects will be examined. All statistics will be done using SPSS V.20.0 and GraphPad Prism. A p-value of less than 0.05 is considered statistically significant.

Dissemination

Study data will be stored in the data centre of CIRO+. The investigator will ensure that all data in the data centre are accurate and is responsible for the monitoring of the data collection. Results will be presented at (inter)national conferences and will be submitted for publication in peer-reviewed journals. Participants are given the opportunity to be informed about the results of the study.

DISCUSSION

The current study is designed to study the validity and responsiveness to pulmonary rehabilitation of CAT in a Dutch population. Initially, the clinical, (patho)physiological and psycho-social determinants of CAT and impact of cardiovascular comorbidities on health status in tertiary care patients with COPD will be examined. In addition, reference values for the CAT will be developed by comparing COPD patients with Dutch elderly non-COPD. The strengths and limitations of the current study are described below.

Strengths

In the current literature, most COPD studies focus on patients from secondary care or tertiary care (30). To our knowledge, this is the first study including patients with COPD treated in primary care as well as patients with COPD treated in secondary and tertiary care. In addition, the current study includes non-COPD subjects enabling a comparison between primary, secondary and tertiary care patients and non-COPD subjects, regarding e.g. health status, mood status and functional status. Consequently, reference values for the CAT in Dutch elderly non-COPD subjects can be determined. Additionally, the majority of the measurements will be done with the same devices. This provides a high reliability, despite the fact that the measurements will be carried out at different places. Furthermore, inter-observer bias will be minimized, because all measurements in non-COPD subjects, primary care and secondary care patients will be performed by one researcher. Furthermore, as mentioned before, patients with COPD have a two- to threefold higher chance to develop cardiovascular morbidity and mortality risk than people without COPD (11) underlying the importance to assess these comorbid conditions carefully. The current study is the first investigating a wide range of (extra)pulmonary parameters providing the possibility to study the individual effect of cardiovascular comorbidities on outcomes, e.g. health status. Finally, patients are recruited from eight different GP practices (RNH affiliated), an academic hospital and a pulmonary rehabilitation centre (CIRO+) increasing the internal and external validity.

Limitations

The results of the current study will be subject to several limitations. *First*, the study sample consists of a convenience sample: possibly in all four healthcare groups the patients with more symptoms, lack of motivation or more severe COPD are less willing to participate in the study, which can lead to selection bias. Consequently, outcomes can be more favourable. To limit selection bias as much as possible, every eligible non-COPD subject, primary care patient and secondary care patient will be approached to participate in the current study by their GP or chest physician, respectively. *Second*, health status may seem a subjective measure. Questionnaires addressing health status usually look at

the emotional, psychological and physical effect of a disease. Measuring health status implies quantifying the impact of the illness on health, wellbeing and daily life, in a standardized and objective manner. According to Jones, the end product doesn't give a clinical impression, because an impaired health status may express itself differently in each patient. However, these questionnaires make it possible to compare health status in patients with COPD (31). *Third*, spirometry will not be performed with the same devices. The spirometry performed in tertiary patients with COPD will be done at CIRO+ as a part of their usual care with the standardized spirometer equipment of Masterlab. However, this device is not portable, making it impossible to be taken to home visits. Therefore, the SpiroPro Viasys will be used to measure lung function in non-COPD subjects and primary and secondary care patients. Both devices are valid and reliable instruments (32, 33) and are currently used in COPD studies (34, 35). The choice is made to perform only one measurement method per person, to decrease the risk of adverse effects (like exhaustion). Subsequently, it is important to consider that spirometry is mainly performed to confirm or exclude diagnoses in the different populations. FEV1 or FEV1/FVC are no outcome parameters in the current study. *Fourth,* comorbidities are extensively assessed in tertiary care. Comprehensive comorbidity assessment is not being undertaken for non-COPD subjects, primary and secondary care COPD patients. These groups only completed the Charlson comorbidity index. *Finally*, measurements in primary and secondary care patients as well as non-COPD subjects will only be conducted cross-sectionally, not providing the possibility to determine causality.

Clinical consequences

The current study is very likely to have clinical implications. Initially, it will give more insight in understanding the systemic effects of COPD, especially the impact of cardiovascular comorbidities on health status. By performing an echocardiography, we will be able to examine cardiac abnormalities, e.g. an impaired systolic left ventricular function, valvular abnormalities or increased right ventricular pressures in relation to clinical outcomes in COPD. This will enable better monitoring of patients and ensure patient safety during pulmonary rehabilitation. Ultimately, patients at risk can receive more

personalized, predictive, preventive and participatory (P4 medicine) care, e.g. to prevent a worsening and/or optimize health status (36). In addition, the current study will examine whether the CAT is a valid measurement to assess health status in Dutch patients and local reference values for clinical practice will be developed. Moreover, by comparing non-COPD subjects and primary, secondary and tertiary care COPD patients, this study will increase our understanding of similarities and differences between the various health care categories in the Netherlands.

Conclusion

To conclude, health status is an important patient-related outcome in COPD. Thus, understanding the validity, responsiveness and clinical determinants of the COPD assessment test (CAT) is essential for the management of patients with this disease. The Chance study will greatly extend the current knowledge on CAT in patients with COPD and non-COPD. In this article the study protocol is described and possible strengths and limitations are outlined.

Footnotes

Contributors DES, SW, EFMW, FMEF and MAS contributed to the conception and design, interpretation of the data, writing the manuscript, critical revision and final approval of this version to be published. JWMM contributed to the recruitment of the subjects, critical revision and final approval of this version to be published. PWJ contributed by interpreting the data, critical revision and final approval of this version to be published.

All authors read and approved the final version.

Funding The CAT study was supported by the Lung Foundation Netherlands (3.4.10.015) and GlaxoSmithKline (SCO115406).

Competing interests None

Patient consent Obtained

Ethics approval The Medical Ethical Committee of the Maastricht University Medical Centre+ (MUMC+), Maastricht, the Netherlands (METC 11-3-070) has approved this study. The study has been registered at the Dutch Trial Register (NTR 3416).

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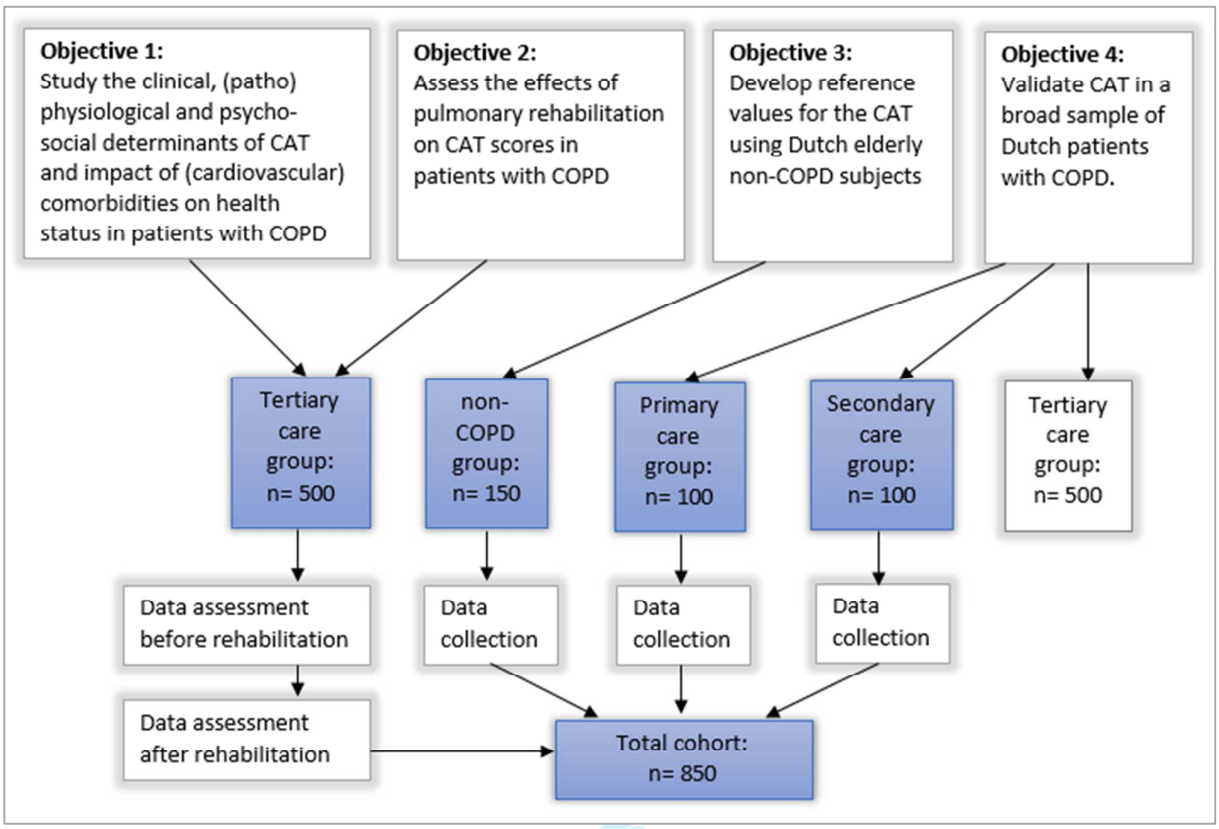

Figure 1. Flow diagram of subject participation and data assessment

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3 and 4
Objectives	3	State specific objectives, including any pre-specified hypotheses	Page 4
Methods			
Study design	4	Present key elements of study design early in the paper	Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4, 5 and 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Page 6 and 7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Inapplicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 7 and 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5, 6, 7 and 8
Bias	9	Describe any efforts to address potential sources of bias	Page 10 and 11
Study size	10	Explain how the study size was arrived at	Inapplicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Inapplicable
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	Page 8 and 9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	Inapplicable
		(*e*) Describe any sensitivity analyses	Page 9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Inapplicable, study not yet performed
		(b) Give reasons for non-participation at each stage	Inapplicable, study not yet performed
		(c) Consider use of a flow diagram	Page 16
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Inapplicable, study not yet performed
		(b) Indicate number of participants with missing data for each variable of interest	Inapplicable, study not yet performed
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	Page 7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	Inapplicable, study not yet performed
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Inapplicable, study not yet performed
		Cross-sectional study—Report numbers of outcome events or summary measures	Inapplicable, study not yet performed
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Inapplicable, study not yet performed
		(*b*) Report category boundaries when continuous variables were categorized	Inapplicable, study not yet performed
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Inapplicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Inapplicable, study not yet performed
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 11 and 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

Outcomes	Non-COPD	Primary care	Secondary care	Tertiary care (pre rehabilitation)	Tertiary care (post rehabilitation)
Demographics, including age, gender, height, weight, marital status, ethnic origin.	Y	Y	Y	Y	Y
Smoking history: current smoking and pack years	Y	Y	Y	Y	Y
Medical history, including current medication	Y	Y	Y	Y	N
COPD history: number of exacerbations and hospitalisations for COPD (<12 months)	Y	Y	Y	Y	Y
Use of long-term oxygen or non-invasive ventilation	Y	Y	Y	Y	Y
Lung function: post-bronchodilator (salbutamol) spirometry measured by a handheld SpiroPro Viasys	Y	Y	Y	N	N
Lung function: post-bronchodilator (salbutamol) spirometry measured by standardized equipment of Masterlab®, Jaeger, Germany whole-body plethysmography, diffusing capacity for carbon monoxide (31)	N	N	N	Y	Y
Degree of self-perceived physical and psychological symptoms [a]	Y	Y	Y	Y	N
Physical examination including vital signs: pulse, blood pressure, saturation	Y	Y	Y	Y	Y
Charlson co-morbidity index **(21)**	Y	Y	Y	Y	Y
Modified Medical Research Council (mMRC) dyspnoea grading **(22)** and New York Heart Association (NYHA) Functional Classification **(23)**	Y	Y	Y	Y	Y
Health status questionnaires: SGRQ-C, CAT, and CCQ **(24)**.	Y	Y	Y	Y	Y
Hospital Anxiety and Depression Scale **(25)**	Y	Y	Y	Y	Y
Daily physical functioning: timed 'up-and-go' test **(26)**	Y	Y	Y	Y	Y
Care Dependency Scale **(27)**	Y	Y	Y	Y	Y
Coping strategies: Utrecht Coping List (37)	N	N	N	Y	Y
Body composition: fat-free mass, fat mass using bioelectrical impedance assessment **(28)**	Y	Y	Y	Y	N
Body composition: whole-body/local dual energy x-ray absorptiometry (DEXA) scan (32)	N	N	N	Y	Y
Systemic inflammation: hsCRP	N	N	N	Y	Y
Six Minute Walk test (2x at baseline) (33)	N	N	N	Y	Y
Constant work-rate bicycle test (34) and cardio pulmonary exercise test	N	N	N	Y	Y
Daily physical activity level using a validated accelerometer (35)	N	N	N	Y	Y
Problematic activities of daily life: Canadian Occupational Performance Measure (36)	N	N	N	Y	Y
Lower-limb muscle function: peak isokinetic quadriceps strength using a biodex (38)	N	N	N	Y	Y
Echocardiography	N	N	N	Y	N
Electrocardiography (39)	N	N	N	Y	Y
NT-proBNP and other cardiovascular markers (to be determined)	N	N	N	Y	Y
Biomarkers metabolic syndrome (40): fasting glucose, cholesterol, HDL, LDL, triglycerides	N	N	N	Y	Y

Y = measurement conducted
N = measurement not conducted
[a] Patient-completed checklist referring to dyspnoea, fatigue, cough, muscle strength, appetite, insomnia, depression, anxiety, panic attacks, pain, mouth soreness, itching, edema, thirst, muscle cramps, restless legs, dizziness, pain on the chest and frequency of urination with visual analogue scales to score the severity of the complaint (questionnaire is approved by the Medical Ethical Committee of the Maastricht University Medical Centre, METC 07-3-054).

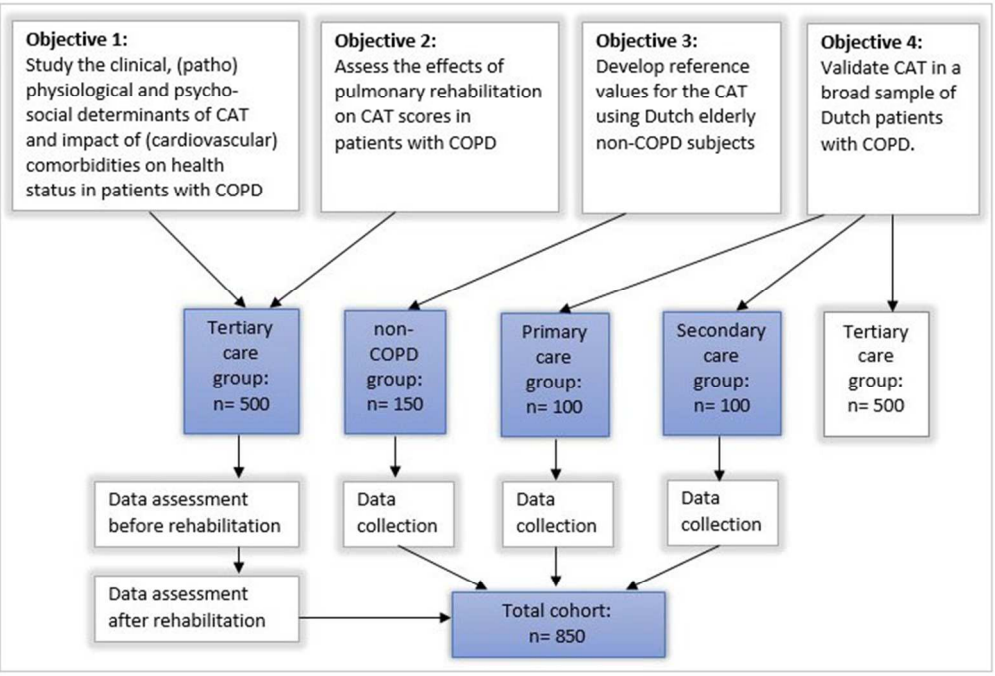

Figure 1. Flow diagram of subject participation and data assessment
60x41mm (300 x 300 DPI)

SAMPLE SIZE CALCULATION

The original sample size calculation:

A sample size calculation for continuous response variables was performed with the available data from literature (Jones et al. Eur Respir Journal 2009). Three sample size calculations were performed, due to the differences in CAT scores were expected to be different between tertiary care COPD patients; tertiary care COPD patients and, primary care and secondary care COPD patients; and tertiary care COPD patients and non-COPD controls.

The mean of non-COPD controls is estimated on 5 units of the CAT. A minimal difference of 5 units with COPD patients resulted that the lowest mean of the CAT for COPD patients should be 10 units (this is a proportion of 0.25 of the maximum of 40 units of the CAT).

Sample size calculation for tertiary care COPD patients:

The sample size calculation to compare tertiary care patients is based on detecting a minimal difference of 4 units of the CAT (4/40 is a proportion of 0.10 of the maximum of 40 units of the CAT).

For this sample size calculations was used:

Power $1-\beta = .80$

Significance level $\alpha = .05$

Formula:

$N = \{(z_{\alpha/2} + z_{1-\beta})^2 * p_{mean} * (1- p_{mean})* (1+r)\}/ \{d^2 * r\}$

$z_{\alpha/2} = 1.96$ (for two sided $\alpha = 0.05$)

$z_{1-\beta} = 0.84$ (for $1-\beta = 0.80$)

$p_{mean} = (r * p_{copd\ patient} + p_{copd\ patient})/(r+1)$ gives $(1* 0.25 + 0.25)/(1+1)= 0.25$

$p_{copd\ patient} = 0.25$

difference d = 0.10

ratio r = 1

$N = \{(1.96 + 0.84)^2 * 0.25 * (1- 0.25) * (1+1)\}/(0.10^2 *1)$ resulted in an n = 294 ≈300. So, the total tertiary care patients group should consist 2 *300 tertiary care patients. The GOLD II and GOLD III tertiary care patients group will consist in 300 patients and the GOLD IV tertiary care patients will also consist of 300 patients.

Sample size calculation for comparing primary care and secondary care COPD patients with tertiary care COPD patients

The sample size calculation to compare tertiary care patients with primary care and secondary care is based on detecting a minimal difference between 4.5 and 5 units of the CAT (4.5/40 is a proportion of 0.11 of the maximum of 40 units of the CAT and 5/40 is a proportion of 0.13 of the maximum of 40 units of the CAT).

For the sample size calculation with 4.5 units difference was used:

Power $1-\beta = .80$

Significance level $\alpha = .05$

Formula:

$N = \{(z_{\alpha/2} + z_{1-\beta})^2 * p_{mean} * (1- p_{mean})* (1+r)\}/ \{d^2 * r\}$

$z_{\alpha/2} = 1.96$ (for two sided $\alpha = 0.05$)

$z_{1-\beta} = 0.84$ (for $1-\beta = 0.80$)

$p_{mean} = (r * p_{copd\ patient} + p_{copd\ patient})/(r+1)$ gives $(1* 0.25 + 0.25)/(1+1)= 0.25$

$p_{copd\ patient} = 0.25$

difference d = 0.11

ratio r = 1

$N = \{(1.96 + 0.84)^2 * 0.25 * (1- 0.25) * (1+1)\}/(0.11^2 *1)$ resulted in an n = 232.3 ≈235

For the sample size calculation with 5 units difference was used:

Power $1-\beta = .80$

Significance level $\alpha = .05$

Formula:

$N = \{(z_{\alpha/2} + z_{1-\beta})^2 * p_{mean} * (1- p_{mean})* (1+r)\}/ \{d^2 * r\}$

$z_{\alpha/2} = 1.96$ (for two sided $\alpha = 0.05$)

$z_{1-\beta} = 0.84$ (for $1-\beta = 0.80$)

$p_{mean} = (r * p_{copd\ patient} + p_{copd\ patient})/(r+1)$ gives $(1* 0.25 + 0.25)/(1+1)= 0.25$

$p_{copd\ patient} = 0.25$

difference d = 0.13

ratio r = 1

$N = \{(1.96 + 0.84)^2 * 0.25 * (1- 0.25) * (1+1)\}/(0.13^2 *1)$ resulted in an n = 188.2 ≈190.

The total tertiary care COPD patients group and the combination of the primary care and secondary care COPD patients consist between 190 and 235 patients for this analyse. Therefore for this study 200 primary care and secondary care COPD patients will be included. A sample of the tertiary care patients of 200 patients will be used for these analyses.

Sample size calculation for comparing non-COPD controls with tertiary care COPD patients

The sample size calculation is based on detecting a minimal difference of 5 units of the CAT (5/40 is a proportion of 0.125 of the maximum of 40 units of the CAT) between COPD patients (3 groups) and non-COPD controls (2 groups). The sample size calculation is repeated with COPD patients as one group and non-COPD controls as one group.

The mean of non-COPD control is estimated on 5 units of the CAT. A minimal difference of 5 units with COPD patients resulted that the lowest mean of the CAT for COPD patients should be 10 units (this is a proportion of 0.25 of the maximum of 40 units of the CAT).

For this sample size calculations was used:

Power $1-\beta = .80$

Significance level $\alpha = .05$

Formula:

$N = \{(z_{\alpha/2} + z_{1-\beta})^2 * p_{mean} * (1- p_{mean})* (1+r)\}/ \{d^2 * r\}$

$z_{\alpha/2} = 1.96$ (for two sided $\alpha = 0.05$)

$z_{1-\beta} = 0.84$ (for $1-\beta = 0.80$)

$p_{mean} = (r * p_{copd\ patient} + p_{non\text{-}copd\ control})/(r+1)$ gives $(1.5* 0.25 + 0.125)/(1.5+1)= 0.5/2.5 =0.20$

$p_{copd\ patient} = 0.25$

$p_{non\text{-}copd\ control} = 0.125$

difference $d = 0.25 - 0.125 = 0.125$

ratio $r = 1.5$

$N = \{(1.96 + 0.84)^2 * 0.20 * (1- 0.20) * (1+1.5)\}/(0.125^2 *1.5)$ resulted in an $n = 133.8 \approx 134$. Based on this calculation the total non-COPD control group should consist 134 participants and the total COPD group should consist $1.5*133.8 = 200.7 \approx 201$ patients.

For this sample size calculations was used:

Power $1-\beta = .80$

Significance level $\alpha = .05$

Formula:

$N = \{(z_{\alpha/2} + z_{1-\beta})^2 * p_{mean} * (1- p_{mean}) * (1+r)\}/ \{d^2 * r\}$

$z_{\alpha/2} = 1.96$ (for two sided $\alpha = 0.05$)

$z_{1-\beta} = 0.84$ (for $1-\beta = 0.80$)

$p_{mean} = (r * p_{copd\ patient} + p_{non\text{-}copd\ control})/(r+1)$ gives $(1* 0.25 + 0.125)/(1+1)= 0.375/2 =0.19$

$p_{copd\ patient} = 0.25$

$p_{non\text{-}copd\ control} = 0.125$

difference d = 0.25 - 0.125 = 0.125

ratio r = 1

$N = \{(1.96 + 0.84)^2 * 0.19 * (1- 0.19) * (1+1)\}/(0.125^2 *1)$ resulted in an $n = 152.88 \approx 153$. Based on this calculation the total non-COPD control group should consist 153 participants and the total COPD group should consist 153 patients.

The total tertiary care COPD patients group and the non-COPD control group should consist between 134 and 153 patients for this analyse. Therefore for this study 150 non-COPD controls will be included. A minimum sample of 150 tertiary care patients will be used for these analyses.

Adjustments to the sample size calculation:

There are some concerns regarding the initial sample size calculation. The following reasons underline the adequacy and sufficiency of a smaller sample size, regarding tertiary care patients (n=500), for the current study.

1. The sample size calculation was based on the out-dated international COPD GOLD 2007 guideline which classified COPD patients into four groups (GOLD I to IV), based on the degree of airflow limitation. However, the 2011 GOLD strategy started classifying patients in four groups based on the combination of the degree of airflow limitation and the number of exacerbations in the past twelve months and health status/severity of symptoms. This new classification has further been elaborated and described in the latest WHO COPD GOLD 2015 document. Consequently, these substantial changes impact the original foundation of the subgroups: it was outdated and a new composition was necessary.

2. One objective of the current study is to study the impact of cardiovascular comorbidities on CAT-scores. An interim analyses showed that a sample size between n=4322 and n=46044 was necessary to detect differences in CAT-scores between patients with and without cardiovascular comorbidities (table 1). However, this sample size is not reasonable and it is not meaningful for the current study to include 600 patients anymore.

Table 1. Sample size calculation based on available data (baseline data of tertiary care patients)

	n	Baseline CAT-score (mean)	Baseline CAT-score (standard deviation)
Cardiovascular comorbidity	192	21.13	6.77
No cardiovascular comorbidity	221	21.63	6.55
Total sample size	**4322**		
Impaired ejection fraction	65	21.54	7.11
No impaired ejection fraction	350	21.38	6.56
Total sample size	**46044**		

The sample size has been calculated with the program G*power 3.1.9. [Friedman et al. "Fundamentals of Clinical Trails" (3rd edition) 1998; Faul et al. Behavior Research Methods 2007].

The performed test is: t-test mean difference between two independent means (two groups) with a power of 0.80 and α-error: 0.05.

3. Furthermore, a minimal clinically important differences of 2 points for the CAT has been established (Kon et al. Lancet Respir Med 2014). This was not available at the time of the initial sample size calculation. A second interim analyses revealed that GOLD II, GOLD III and GOLD IV patients following rehabilitation showed a clinically relevant improvement of their health status (table 2). Thus, it is possible to detect clinically relevant changes with the present available data.

Table 2. Sample size calculation based on available data (change in CAT-score, longitudinal data (before and after rehabilitation) of tertiary care patients

GOLD stage	n	Change in CAT score (mean)	Change in CAT score (standard deviation)
2	95	-2.61	6.94
3	102	-3.50	6.88
4	56	-2.98	7.69

4. However, using these data (table 2) to re-calculate the sample size, a sample of n=3084 was needed (table 3). This is due to small differences in variances. As mentioned earlier, this sample size is not reasonable and meaningful for the current study.

Tabel 3. Sample size calculation based on available data (change in CAT-score, longitudinal data (before and after rehabilitation) of tertiary care patients

GOLD stage	n	Change in CAT score (mean)	Change in CAT score (standard deviation)	
2	95	-2.61	6.94	
3	102	-3.50	6.88	
4	56	-2.98	7.69	
Between variance				39.260
Within variance				12553.072
Total sample size	**3084**			

The sample size has been calculated with the program G*power 3.1.9. [Friedman et al. "Fundamentals of Clinical Trails" (3rd edition) 1998; Faul et al. Behavior Research Methods 2007].

The performed test is: F-test; ANOVA: fixed effects omnibus, one-way, with a power of 0.80 and α-error: 0.05.

5. During the period we requested approval of the local medical ethical committee to adjust the sample size calculation, nearly 500 tertiary care patients were included in the study. Due to the unfeasible amount of patients needed after a re-calculation of the sample size, we

suggested a study sample of 500 patients. Some observational research has been published studying the change of CAT in patients with COPD following pulmonary rehabilitation. The sample sizes in these studies varied between n=118 and n= 377 (e.g. Dodd et al. Thorax 2011, Dodd et al. COPD 2012, Kon et al. Respiration 2013) underlying the sufficiency of 500 patients for the current study.